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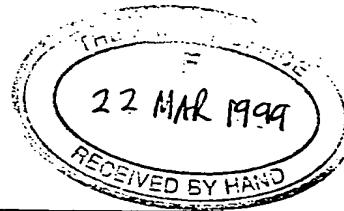
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MPW/P21497GB

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9906587.2

22 MAR 1999

3. Full name, address and postcode of the or of each patent applicant (underline all surnames)

CHARTERHOUSE THERAPEUTICS LTD.
15 CITY BUSINESS CENTRE
HYDE STREET
WINCHESTER
HAMPSHIRE SO23 7TA
UK

Patents ADP number (if you know it)

7626732001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

CHEMICAL COMPOUNDS AND THEIR USES

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

see 5.177.

KILBURN & STRODE
20 RED LION STREET
LONDON
WC1R 4PJ

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The Old College
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Kilburn & Strode
Kilburn & Strode *M. White*

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22 March 1999

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Martin P White
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Chemical compounds and their uses

The present invention relates to chemical compounds and their uses. More particularly, the present invention relates to cyclopentenones and to their uses in medicine.

5 Various compounds comprising the cyclopentenone ring structure (also known as the cyclopentenone nucleus) are capable of inducing the heat shock response. The heat shock response is a finely regulated and highly conserved mechanism to protect cells

10 against different types of injury, including extreme temperatures, oxidative stress, exposure to toxins and viral infection (1). In human cells, triggering of the heat shock response requires activation of a transregulatory protein, the heat shock transcription factor type 1 (HSF 1), which controls the expression of cytoprotective heat shock proteins (HSPs) (1). Whereas HSP induction was at first interpreted as a signal for

15 detection of physiological stress, it is now accepted that HSPs are utilised by the cells as molecular chaperones in the repair process following different types of injury to prevent damage resulting from the accumulation and aggregation of non-native proteins (1). In particular a cytoprotective role of the heat shock protein HSP70 has now been described in a wide variety of human diseases, including ischemia,

20 inflammation and viral infection (2-5). For these reasons HSF 1 is considered a novel, attractive target for cytoprotective and antiviral drugs. In the case of viral infection, Santoro *et al.* have shown that a class of prostaglandins (PGs) with potent antiviral activity function as HSP70 inducers via HSF1 activation (6,7).

25 The ability of prostaglandins of the A type (PGAs) to inhibit virus replication and prevent the establishment of persistent infections was first reported in 1980 (8). It is now well established that PG containing an α,β -unsaturated carbonyl group in the cyclopentane ring structure (cyclopentenone PG, cyPG) possess activity against a wide variety of DNA and RNA viruses, including herpes viruses, paramyxo viruses,

orthomyxo viruses and retroviruses in *in vitro* and *in vivo* experimental models (9). The mechanism of the antiviral activity is distinct from any other known antiviral agent and involves the induction of heat shock proteins and the inhibition of the transcription factor NF- κ B (nuclear factor- κ B) in the infected cell.

5

NF- κ B is an inducible eukaryotic transcription factor which has a critical role in promoting inflammation and viral replication (11). In most cells NF- κ B exists in an inactive cytoplasmic complex, whose predominant form is a heterodimer composed of p50 and p65 subunits, bound to inhibitory proteins of the I κ B family, usually I κ B α , and is activated in response to primary (viruses, bacteria, UV) or secondary (inflammatory cytokines) pathogenic stimuli (12). Stimulation triggers rapid phosphorylation and degradation of I κ B α , resulting in NF- κ B translocation to the nucleus, where the factor binds to DNA at specific κ B-sites, inducing a variety of genes encoding signalling proteins. Target genes include inflammatory and chemotactic cytokines, cytokine receptors and viral genes. NF- κ B is involved in many pathological events including progression of AIDS by enhancing HIV-1 transcription, and is considered an attractive therapeutic target for novel antiviral and anti-inflammatory drugs (12). Santoro *et al.* have shown that cyclopentenone prostaglandins inhibit NF- κ B activation and NF- κ B-dependent HIV-1 transcription in human cells, by preventing I κ B α phosphorylation and degradation, and that this effect is strictly associated with HSF1 activation (11).

10

15

20

25

Santoro *et al.* have identified the molecular structure of natural prostaglandins responsible for HSF activation and NF- κ B inhibition (13). One component of the PGA molecule, cyclopent-2-en-1-one (also known as 2-cyclopenten-1-one), at a concentration of 125-500 μ M, has been shown to be able to activate HSF1 and to rapidly and selectively trigger the synthesis of cytoprotective HSP70. At the same concentration, cyclopent-2-en-1-one has been shown to be able to block NF- κ B

activation by chemical or physiological inducers. These effects are associated with antiviral activity during infection with rhabdoviruses (13).

5 The present inventors have now identified compounds that have surprisingly high activity (relative to cyclopent-2-en-1-one) in various assays that are described in Examples 1 to 3.

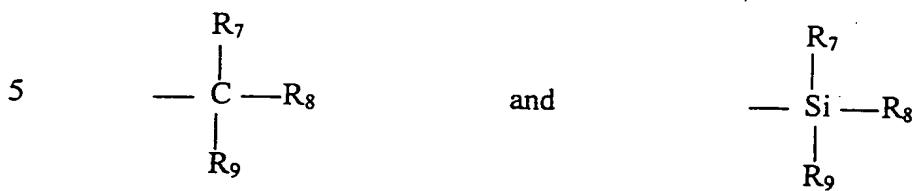
10 According to the present invention there is provided a compound for use in medicine, that has the formula a), b), c) or d), as shown in Figure 1; wherein R₁, R₂, R₃, R₄, R₅ and R₆ can (independently) be hydrogen or any other appropriate moiety.

15 R₁, R₂, R₃ and R₄ may, for example, (independently) be hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group. Where a plurality of carbon atoms are present in any of R₁, R₂, R₃ or R₄ it is preferred that between 2 and 20 (more preferably 20 between 3 and 15) carbon atoms are present. R₁, R₂, R₃ and R₄ may comprise cyclic or non-cyclic groups. A functional group (e.g. a carboxylic acid group) may be included.

25 R₅ and R₆ may, for example, (independently) be hydrogen or halogen.

X may be any moiety. Preferably however it is an Si-containing or C-containing group. Most preferably it is an Si-containing group.

X therefore includes:



10 wherein R_7 , R_8 and R_9 are defined as for R_1 , R_2 , R_3 and R_4 above, but are preferably alkyl, substituted alkyl, aryl or substituted aryl.

15 Preferably X is hydrophobic and/or lipophilic. It may, for example, have only 1, 2 or 3 carbon atoms. Desirably, however, it comprises at least 4 carbon atoms. A maximum number of carbon atoms for X has not been determined. However, without being bound by theory, it is envisaged that compounds with up to 20 carbon atoms (more preferably up to 12 carbon atoms) will normally be used in the present invention.

20 It is important to note that compounds for use in the present invention do not require the presence of the long aliphatic lateral side chains that are present in those prostaglandins or punaglandins that have a cyclopentenone ring structure (sometimes referred to as a cyclopentenone nucleus). Thus one or more such side chains may be absent at the 4 and/or 5 positions of the cyclopentenone ring. The known punaglandin derivative shown in Figure 3b) has such a side chain and is expressly disclaimed from the scope of the present invention.

25 If a side chain is present at positions R_3 and/or R_4 shown in Figure 1, then preferably it has no more than 7 carbon atoms. More preferably it has no more than 3 carbon atoms. However it is most preferred that R_3 and/or R_4 are hydrogen.

From the foregoing description it will be appreciated that compounds of the present invention includes various 4- and 5-oxacyclopent-2-en-1-ones. An oxa moiety (provided by -O-X) may be present at both 4 and 5 positions of the cyclopentenone ring. The -O-X group may be provided twice at the 4 position and/or at the 5 position, if desired.

Preferred compounds for use in the present invention have higher activity than cyclopent-2-en-1-one in respect of one or more of the following:

- 10 a) activating HSF
- b) inhibiting NF- κ B
- c) inhibiting the replication of HSV-1
- d) inhibiting the replication of Sendai virus.

15 Activity can be assayed by following the procedures set out in Example 1 (for a) and b)), in Example 2 (for c)) or in Example 3 (for d)).

Increased activity relative to cyclopent-2-en-1-one need not exist at all concentrations. It is however preferred that it exists over a range of 1 - 200 μ M or over at least part of 20 said range.

Preferably a level of activity can be obtained using compounds of the present invention that is at least twice the level of cyclopent-2-en-1-one. More preferably it is at least 10 times that of cyclopent-2-en-1-one.

25 Particularly preferred compounds for use in the present invention include the R and S enantiomers of 4-tert-butyldimethyl siloxy-cyclopent-2-en-1-one (see Figures 2a) and 2b) respectively).

Both forms have unexpectedly high levels of activity, being at least 100 times more effective in activating HSF and inhibiting NF- κ B than cyclopent-2-en-1-one. It is particularly surprising that the S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one enantiomer is so active, given that this isomeric form does not correspond with the 5 form of prostaglandins that occurs in nature (the R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one form).

In view of these findings, both R- and S-enantiomers of all compounds described in connection with the present invention are considered useful and may each be provided 10 in a form substantially free of the other enantiomer (e.g. at least 75% free (w/w), at least 90% free (w/w) or at least 99% free (w/w)). Mixtures of these enantiomers (e.g. racemic mixtures) may however be used if desired.

Certain findings in respect of the present invention may be explained by a theory 15 referred to as the "anchor theory", which is provided for the first time below. It is however important to note that the present invention does not rely upon this theory and therefore if it turns out to be incorrect this has no bearing upon the validity of the present invention.

20 **Anchor theory**

The active part of prostaglandin molecules that stimulate HSP and inhibit NF- κ B is the cyclopentenone ring structure. This is present in two classes of prostaglandins: the PGA series (see Fig 4a) and the PGJ series (see Fig 4b).

25

In summary, the anchor theory is that *in vivo* the cyclopentenone nucleus is put in place at or in close proximity to the active site of a receptor by a side chain anchoring it to a hydrophobic domain of a receptor. The cyclopentenone nucleus can associate with and dissociate from the active site of the receptor. The probability of association

and/or the duration of association may be higher when a hydrophobic anchor is present. The presence of a side chain at the S-position (see Fig 4c) may provide an improved anchoring effect (see Fig 4d). A similar effect is believed to occur with the Salbutamol derivative Salmeterol, which has a lipophilic "anchoring" side chain that aids binding and increases its effect on the target β -receptors.

5 ***A) Medical Uses***

10 Compounds of the present invention may be used for any desired therapeutic purpose. Preferred treatments are human treatments, although veterinary treatments are also within the scope of the present invention. The treatment may be prophylactic or may be in respect of an existing condition.

15 Treatments are desirably of disorders which can be treated in a host by the activation of a heat shock transcription factor (e.g. HSF1), by the induction of heat shock proteins (e.g. hsp70) and/or by the inhibition of NF- κ B.

20 Various preferred treatments are discussed below. (It should be appreciated that certain disorders - e.g. cancers - may be mediated both by viruses and by non-viral factors. In the absence of any indication to the contrary, treatment of any given disorder is covered whether or not the disorder is mediated by viruses. It should also be appreciated that there is some overlap between the various categories of treatment discussed - i.e. the categories are not intended to be mutually exclusive.)

25 1. *Treatment of viral-mediated disorders*

NF- κ B is implicated in the pathogenesis of certain viral infections. It is known that heat shock proteins (e.g. HSP70) can offer protection against the pathogenesis of viral

infection. Furthermore, it has now been shown that compounds of the present invention are surprisingly active in reducing the replication of viruses.

Compounds of the present invention are therefore useful in treating viral-mediated
5 disorders. These include disorders mediated by RNA viruses (which may be single-stranded, negatively polarised RNA viruses), as well as disorders mediated by DNA viruses.

10 Examples of viral disorders that can be treated using compounds of the present invention include disorders mediated by: retroviruses (e.g. HIV1), herpes viruses (e.g. HSV-1, CMV, HHV8, HSV-2), paramyxo and orthomyxo viruses (as illustrated by Sendai viruses and including influenza viruses), rhabdoviruses (e.g. vesicular stomatitis virus, rabies viruses), picornaviruses (e.g. rhinoviruses and hepatitis A viruses), hepadnaviruses (e.g. hepatitis B viruses), togaviruses (e.g. rubella viruses), or poxviruses (e.g. molluscum 15 contagiosum virus).

Additional viral disorders that can be treated using compounds of the present invention include: filoviruses (e.g. Ebola virus), bunyaviruses (e.g. hantaviruses), arenaviruses (e.g. lassa fever virus), flaviviruses (e.g. yellow fever and hepatitis C viruses).

20

2. *Treatment of bacterial-mediated disorders*

NF- κ B is activated in response to bacterial infections.

25 Compounds of the present invention are useful in treating disorders arising from such infections - e.g. in treating NF- κ B stimulated inflammation. Most commonly this will arise due to infection with Gram negative bacteria. However it may also arise due to infection with Gram positive bacteria (e.g. *S. aureus*).

3. *Treatment of disorders mediated by radiation*

NF- κ B is activated in response to radiation (e.g. UV-radiation).

5 Compounds of the present invention are therefore useful in treating disorders mediated by radiation. Such disorders include cell and tissue trauma, cell and tissue ageing and cancer (e.g. skin cancer).

4. *Treatment of inflammation and of disorders of the immune system*

10

NF- κ B is activated in response to inflammatory cytokines. It is believed to be an early mediator of the immune and inflammatory responses.

15 Compounds of the present invention are useful in treating immune disorders (e.g. auto-immune disorders) and in treating inflammatory disorders.

20 Examples of specific inflammatory disorders and disorders of the immune system that can be treated with compounds of the present invention include rheumatoid arthritis, multiple sclerosis, adult respiratory distress syndrome, hepatitis and/or cirrhosis, vascular inflammation (including lupus erythematosus disseminata), and inflammatory disorders of the gastro-intestinal tract (e.g. ulcers).

5. *Treatment of Ischemia and Arteriosclerosis*

25 NF- κ B has been implicated in the pathogenesis of ischemia and arteriosclerosis.

Compounds of the present invention are therefore useful in treating such disorders. These disorders include reperfusion damage (e.g. in the heart and/or brain) and cardiac hypertrophy.

6. *Treatment of disorders involving cell proliferation*

NF- κ B is implicated in cell proliferation.

5

Compounds of the present invention are useful as anti-proliferatives. They are therefore useful in treating, inflammatory granulomas, neointimal proliferation in arterial and venous restenosis, and cancers (including lymphomas, leukemias, sarcomas, carcinomas and melanomas).

10

7. *Treatment of disorders involving damage to or killing of cells*

Heat shock proteins are known to provide a cytoprotective effect.

15 Compounds of the present invention are therefore useful in treating disorders involving damage to or killing of cells.

These disorders include chemical toxicity (e.g. due to ingestion of toxins, such as paraquat, or to overdosing with medicaments, such as paracetamol), oxidative cell 20 damage, cell and tissue ageing, trauma, hepatitis and diabetes.

8. *Other treatments*

25 Cyclopentenone prostaglandins are of known utility in stimulating peroxisome proliferator activated receptors (PPARs). This is a further indication of the utility of compounds of the present invention in treating diabetes (including complications arising therefrom).

A compound of the present invention may be used in the manufacture of a medicament for one or more of the previously mentioned treatments.

5 A medicament will usually be supplied as part of a pharmaceutical composition, which may include a pharmaceutically acceptable carrier. This pharmaceutical composition will generally be provided in a sterile form. It may be provided in unit dosage form. It will generally be provided in a sealed container, and can be provided as part of a kit. Such a kit is within the scope of the present invention. It would normally (although not necessarily) include instructions for use. A plurality of unit dosage forms may be
10 provided.

15 Pharmaceutical compositions within the scope of the present invention may include one or more of the following: preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colourants, odourants, salts (compounds of the present invention may themselves be provided in the form of a pharmaceutically acceptable salt – as explained in greater detail below), buffers, coating agents or antioxidants. They may also contain other therapeutically active agents in addition to a compound of the present invention.

20 Compounds of the present invention may themselves be provided in any suitable form – i.e. they may be used as such or may be used in the form of a pharmaceutically effective derivative. For example they may be used in the form of a pharmaceutically acceptable salt or hydrate. Pharmaceutically acceptable salts include alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts (e.g. calcium or magnesium salts)
25 aluminium salts, zinc salts, ammonium salts (e.g. tetra-alkyl ammonium salts), etc. Inorganic acid addition salts (e.g. hydrochlorides, sulphates, or phosphates) or organic acid addition salts (e.g. citrates, maleates, fumarates, succinates, lactates, propionates or tartrates) may be used.

Pharmaceutical compositions of the present invention may be provided in controlled release form. This can be achieved by providing a pharmaceutically active agent in association with a substance that degrades under physiological conditions in a predetermined manner. Degradation may be enzymatic or may be pH-dependent.

5

Pharmaceutical compositions may be designed to pass across the blood brain barrier (BBB). For example, a carrier such as a fatty acid, inositol or cholesterol may be selected that is able to penetrate the BBB. The carrier may be a substance that enters the brain through a specific transport system in brain endothelial cells, such as insulin-like growth factor I or II. The carrier may be coupled to the active agent or may contain / be in admixture with the active agent. Liposomes can be used to cross the BBB. WO91/04014 describes a liposome delivery system in which an active agent can be encapsulated/embedded and in which molecules that are normally transported across the BBB (e.g. insulin or insulin-like growth factor I or II) are present on the liposome outer surface. Liposome delivery systems are also discussed in US Patent No. 4704355.

10

Routes of Administration

A pharmaceutical composition within the scope of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) routes. Such a composition may be prepared by any method known in the art of pharmacy, for example by admixing one or more active ingredients with a suitable carrier.

15

Different drug delivery systems can be used to administer pharmaceutical compositions of the present invention, depending upon the desired route of administration. Drug delivery systems are described, for example, by Langer (Science 249, 1527 – 1533 (1991)) and by Illum and Davis (Current Opinions in Biotechnology 2, 254 – 259

25

(1991)). Different routes of administration for drug delivery will now be considered in greater detail:

(i) Oral Administration

5

Pharmaceutical compositions adapted for oral administration may be provided as capsules or tablets; as powders or granules; as solutions, syrups or suspensions (in aqueous or non-aqueous liquids); as edible foams or whips; or as emulsions. Tablets or hard gelatine capsules may comprise lactose, maize starch or derivatives thereof, stearic acid or salts thereof. Soft gelatine capsules may comprise vegetable oils, waxes, fats, semi-solid, or liquid polyols etc. Solutions and syrups may comprise water, polyols and sugars. For the preparation of suspensions oils (e.g. vegetable oils) may be used to provide oil-in-water or water-in-oil suspensions.

10 An active agent intended for oral administration may be coated with or admixed with a material that delays disintegration and/or absorption of the active agent in the gastrointestinal tract (e.g. glyceryl monostearate or glyceryl distearate may be used). Thus the sustained release of an active agent may be achieved over many hours and, if necessary, the active agent can be protected from being degraded within the stomach.

20 Pharmaceutical compositions for oral administration may be formulated to facilitate release of an active agent at a particular gastrointestinal location due to specific pH or enzymatic conditions.

(ii) Transdermal Administration

25

Pharmaceutical compositions adapted for transdermal administration may be provided as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis. (Iontophoresis is described in *Pharmaceutical Research*, 30 3(6):318 (1986).)

(iii) Topical Administration

5 Pharmaceutical compositions adapted for topical administration may be provided as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils. For topical administration to the skin, mouth, eye or other external tissues a topical ointment or cream is preferably used. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water 10 base or a water-in-oil base. Pharmaceutical compositions adapted for topical administration to the eye include eye drops. Here the active ingredient can be dissolved or suspended in a suitable carrier, e.g. in an aqueous solvent. Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouthwashes.

15

(iv) Rectal Administration

Pharmaceutical compositions adapted for rectal administration may be provided as suppositories or enemas.

20

(v) Nasal Administration

This includes not only administration to the nasal cavity, but also administration via the nasal cavity to another location – e.g. to the lungs.

25

Pharmaceutical compositions adapted for nasal administration may use solid carriers - e.g. powders (preferably having a particle size in the range of 20 to 500 microns). Powders can be administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nose from a container of powder held close to the nose.

30

Compositions adopted for nasal administration may alternatively use liquid carriers – e.g.

include nasal sprays or nasal drops. These may comprise aqueous or oil solutions of the active ingredient.

5 Compositions for administration by inhalation may be supplied in specially adapted devices – e.g. in pressurised aerosols, nebulizers or insufflators. These devices can be constructed so as to provide predetermined dosages of the active ingredient.

(vi) Vaginal Administration

10 Pharmaceutical compositions adapted for vaginal administration may be provided as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

(vii) Parenteral Administration

15 Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injectable solutions or suspensions. These may contain antioxidants, buffers, bacteriostats and solutes that render the compositions substantially isotonic with the blood of an intended recipient. Other components that may be present in such compositions include water, alcohols, polyols, glycerine and vegetable oils, for example.

20 Compositions adapted for parenteral administration may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, e.g. sterile water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

25

From the above description it will be appreciated that compositions of the present invention can be formulated in many different ways. However preferred compositions of the present invention are in the form of topical formulations.

Dosages

5 Dosages of a compound of the present invention can vary between wide limits, depending upon the nature of the treatment, the age and condition of the individual to be treated, etc. and a physician will ultimately determine appropriate dosages to be used.

10 However, without being bound by any particular dosages, a daily dosage of a compound of the present invention of from 10 μ g to 100mg/kg body weight may be suitable.

15 More preferably the dosage is from 5 to 50 mg/kg body weight/day. The dosage may be repeated as often as appropriate. If side effects develop, the amount and/or frequency of the dosage can be reduced, in accordance with good clinical practice.

15 ***D) Research Uses***

20 A compounds of the present invention are useful in research. For example it can be used as a research tool for the analysis of one or more of the following: HSF, NF- κ B, the heat shock response, viral replication, viral-mediated disorders, bacterial-mediated disorders, disorders mediated by radiation (e.g. by UV-radiation), inflammatory disorders, disorders of the immune system, ischemia, arteriosclerosis, disorders involving cell proliferation (e.g. cancers), disorders involving damage to, or killing of cells (e.g. oxidative cell damage), and diabetes.

25 As will be appreciated from the foregoing description, compounds of the present invention have a variety of different uses. It is however important to note that certain compounds are believed to be novel and are therefore covered *per se*, irrespective of how they may be used.

Such compounds include all compounds described for use in the present invention other than 4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one and 15-deoxy-13,14-dihydroprostaglandin J₂.

The present invention will now be described by way of example only with reference to the accompanying drawings, wherein:

Figures 1a) to d) provide the structures of compounds of the present invention.

5

Figures 2a) and 2b) provide the structures of R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one and S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one respectively (referred to herein as CTC7 and CTC8 respectively).

10 Figure 3a) provides the structure of cyclopent-2-en-1-one (referred to herein as CTC1).

Figure 3b) provides the structure of a punaglandin derivative disclosed in Japanese patent application number JP6205928.

15

Figure 4a) provides the structure of PGA₂.

Figure 4b) provides the structure of PGJ₂.

20 Figure 4c) illustrates the S position of a side chain of a PGA-like molecule.

Figure 4d) illustrates the anchor theory.

25 Figure 5 illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8), R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) and cyclopent-2-en-1-one (CTC1) on the activity of transcription factors HSF and NF-κB.

Figure 6a) illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8), R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) and

cyclopent-2-en-1-one (CTC1) on the replication of Herpes simplex virus type 1.

Figure 6b) provides a comparison of the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8) on HSV-1 replications with that of Aciclovir.

5

Figure 7 illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8), R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) and cyclopent-2-en-1-one (CTC1) on the replication of Sendai virus.

10 Figure 8 illustrates the effect of S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC8) or nitrite formation at submicromolar concentrations. A comparision with PG-J2 is provided.

15 Figure 9 illustrates the effect of R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (CTC7) infusion on the blood pressure of normal Wister rats, CTC8 is compared with the prostaglandin PG-E and with the cyclopentenone prostaglandin PG-A.

ExamplesExample 1: Effect of CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) on the activity of transcription factors HSF and NF- κ B.

5

Methods: Human lymphoblastoid Jurkat T cells were grown at 37°C in a 5% CO₂ atmosphere in RPMI 1640 medium (GIBCO BRL, Gaithersburg, MD) supplemented with 10% fetal calf serum (FCS, Hyclone Europe Ltd, UK), 2 mM glutamine and antibiotics according to the method described by A. Rossi *et al.* (Proc. Natl. Acad. Sci.

10 USA 94: 746-750, 1997). CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) were stored as a 100% ethanolic stock solution (100 mM) and diluted to the appropriate concentration in culture medium at the time of use. Cells were treated with different concentrations of CTC8, CTC7 or CTC1 for 1 hour and then stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA, 25 ng/ml), which is a strong inducer of

15 NF- κ B. Control cells received an equal amount of control diluent. After 3 hours whole-cell extracts were prepared and subjected to analysis of DNA-binding activity by EMSA (Electrophoretic Mobility Shift Assay) for detection of HSF or NF- κ B activation, according to the method described by A. Rossi *et al.* (Proc. Natl. Acad. Sci. USA 94: 746-750, 1997). Specificity of protein-DNA complexes was verified by

20 immunoreactivity with polyclonal antibodies specific for p65 (Rel A) or for HSF-1, for NF- κ B and HSF respectively. Quantitative evaluation of NF- κ B- and HSF- DNA complex formation was determined by Molecular Dynamics PhosphorImager (MDP) analysis and is expressed in arbitrary units, as described in A. Rossi *et al.* (J. Biol. Chem. 273: 16446-16452, 1998).

25 Results from a representative experiment are shown. Each experiment was repeated at least 3 times.

Results and conclusions: The results shown in Fig. 5 indicate that CTC8 and CTC7 are potent inducers of HSF and inhibitors of NF- κ B, with CTC8 being

more active than CTC7. Both compounds are shown to be at least 100 times more effective in activating HSF and inhibiting NF- κ B than the originally described compound cyclopent-2-en-1-one (CTC1).

Example 2: Effect of CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) on the replication of Herpes simplex virus type 1.

5 **Methods:** Human HEp-2 laryngeal carcinoma cells and monkey VERO cells were grown at 37°C under the conditions described in Example 1 for T cells. Cell viability was determined by dye exclusion technique or by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT, Sigma Chemical Co.) to MTT formazan conversion assay, as described by F. Denizot and R. Lang (J. Immunol. Methods 89: 271-277, 1986). Herpes simplex virus type 1 (HSV-1), strain F grown in VERO cells, 10 was used at a multiplicity of infection of 10 plaque forming units (PFU) per cell. Confluent HEp-2 cell monolayers were infected with HSV-1 for 1 h at 37°C. After this time, virus inocula were removed and cells were incubated in RPMI 1640 medium containing 2% FCS. Different concentrations of CTC8, CTC7 or cyclopent-2-en-1-one (CTC1) were added to the culture after the 1 h 15 adsorption period, and maintained in the medium for the duration of the experiment. Control medium contained the same concentration of ethanol diluent, which did not affect cell metabolism or virus replication. HSV-1 virus titres were determined 24 hours after infection by cytopathic effect 50% (CPE50%) assay on confluent VERO cells monolayers in 96-well tissue 20 culture plates (six dilutions for each sample, eight wells for each dilution), as described by F. Pica *et al.* (Antiviral Res. 20: 193-208, 1993). The dilution that gives 50% cytopathic effect was determined by the interpolating procedure of Reed and Muench, as described by E. Rodriguez-Boulan (Methods Enzymol. 98: 486-501, 1983). Results from a 25 representative experiment are shown. Each experiment was repeated at least 3 times.

Results and conclusions: The results shown in Fig. 6a) indicates that CTC8 is a potent inhibitor of HSV-1 virus replication, with an ID₅₀ = 0.2 μM (ID₅₀

= 50% inhibitory dose). The antiviral activity occurs at concentrations non-toxic to the cells, as the LD₅₀ (lethal dose 50%) was determined to be 35 μ M by MTT assay in the same cell line, with a selective index (S.I.) = 175. CTC7 has a weaker antiviral activity than CTC8, with an ID₅₀ = 3 μ M. 5 CTC8 is shown to be at least 100 times more active in reducing HSV-1 yield than cyclopent-2-en-1-one (ID₅₀ = 60 μ M; S.I. = 12.5) and reduces HSV-1 yield by 99.997% at concentrations below the LD₅₀.

10 Figure 6b) provides a comparison of the antiviral activity of CTC8 with that of Aciclovir over a range of concentrations.

Table 1 below provides IC values based upon Figures 6a) to c).

Table 1			
HSV-1	IC50	IC90	IC99
Aciclovir	(0.02 μ M)	0.1 μ M	0.8 μ M
CTC-8	0.2 μ M	0.3 μ M	1.4 μ M

15 (The brackets indicate that the figure is an extrapolated one.)

Example 3: Effect of CTC8, CTC7 and cyclopent-2-en-1-one (CTC1) on the replication of Sendai virus.

5 **Methods:** Monkey kidney 37RC cells were grown at 37°C under the conditions described in Example 1 for T cells. The parainfluenza Sendai virus (SV) was grown in the allantoic cavity of 10-day-old embryonated eggs. Viral titre was expressed in haemagglutinating units (HAU) per ml; haemagglutinin titration was done according to standard procedures using human 0 Rh+ erythrocytes, as described in C. Amici *et al.* (J. Virol. 68: 6890-6899, 1994). Confluent monolayers of 37RC cells were 10 infected with SV virus (5 HAU/10⁵ cells) for 1 h at 37°C, and then treated with different concentrations of CTC8, CTC7 or CTC1. Virus yield at 24 hours after infection was determined in the supernatant of infected cells by HAU titration. Results from a representative experiment are shown. Each experiment was repeated at least 3 times.

15 **Results and conclusions:** The results shown in Fig. 7 indicate that CTC8 is a potent inhibitor of Sendai virus replication, with an ID₅₀ = to 0.1 μM. CTC7 has a weaker antiviral activity than CTC8, with an ID₅₀ = 2 μM. CTC8 is shown to be at least 100 times more active in reducing Sendai virus 20 yield than cyclopent-2-en-1-one (ID₅₀= 90 μM).

Table 2 below provides IC values based upon Figure 7.

Table 2			
Sendai	IC50	IC90	IC99
CTC-8	0.1 μM	1.6 μM	8.3 μM

Example 4: Evidence for anti-inflammatory effects of CTC-8:

Immune cells such as neutrophils and macrophages are activated in response to injury and infection. When activated they produce nitric oxide and superoxide radicals to kill 5 foreign cells and cancer cells. They also produce a variety of cytokines and chemokines to cause further recruitment of immune cells in a cascade leading to the cardinal symptoms of inflammation; heat, redness, swelling, pain, and loss of function.

A key signalling step in the activation of the immune cells is the transcription factor 10 *nuclear factor κB* (NF-κB) (16). NF-κB regulates the transcription of a spectrum of pro-inflammatory genes such as IL-1, IL-2, TNF- α , ICAM-1, VCAM-1, and E-selectin as well as the inducible form of nitric oxide synthase (iNOS) and cyclo-oxygenase II.

15 Thus the activation of NF-κB occupies a critical position in the inflammatory cascade. As cyclopentenone prostaglandins are known to have anti-inflammatory actions (17), the cyclopentenone derivative CTC-8 was tested for its effects on the induction of iNOS in a mouse macrophage model.

20 Mouse macrophages of the cell line RAW264.7 were stimulated with gamma interferon and 0.1 U/ml of bacterial lipopolysaccharide (LPS) in 96-well plates (17). The induction of iNOS was measured by determination of the levels of nitrite (NO₂⁻) formed in the supernatant, using the Griess reagent. The natural cyclopentenone prostaglandin PG-J₂ was used for comparison.

25 CTC-8 had a concentration-dependent inhibitory effect on nitrite formation at submicromolar concentrations (Fig. 8). At a concentration of 3 μ g/ml the level of nitrites was reduced to background levels. PG-J₂ had similar effects but was much less potent. No evidence of cytotoxicity was seen for either CTC-8 or PG-J₂.

The results of this experiment indicated that the induction of the pro-inflammatory iNOS gene by interferon gamma and LPS treatment is suppressed by CTC-8. The most likely explanation is that CTC-8 is inhibiting the activation of the NF- κ B pathway.

5

Table 3 below shows IC50 values obtained for PGJ₂ and CTC-8 in respect of the inhibition of nitrite formation.

Table 3	
INOS	IC50
PG-J2	(11.0 μ g/ml)
CTC-8	0.79 μ g/ml

10 (The brackets indicate that the figure is an extrapolated one.)

Example 5: Evidence that CTC-8 does not lower blood pressure:

Most prostaglandins have strong effects on vascular smooth muscle, and will lower blood pressure in animals and humans. The cyclopentenone derivative CTC-8 was 5 therefore tested for its effect on the blood pressure of the anaesthetized rat. Prostaglandins A₁ and E₁ were used for comparison.

Male Wistar rats were anaesthetized and test drugs were infused intravenously. Blood pressure and heart rate were recorded from the femoral artery

10

Prostaglandins A₁ and E₁ caused dose-dependent falls in blood pressure in doses from 30 μ g/kg/min (Fig. 9). CTC-8 at doses from 60-1200 μ g/kg/min had no effect on blood pressure. At the higher dose a small fall in blood pressure was observed but this was not different from that of solvent alone.

15

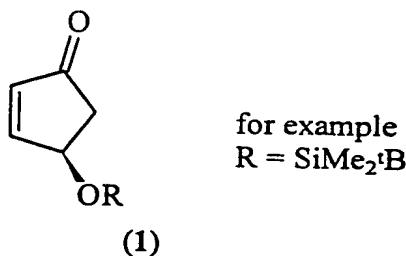
These results indicate that CTC-8 may be devoid of the generalised effects on smooth muscle characteristic of natural cyclopentenone prostaglandins.

20

Example 6: Preparation of compounds of the present invention

Compounds of type (1) are prepared according to literature methods. (18)

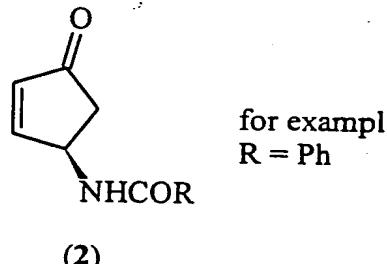
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Compounds of type (2) are prepared as illustrated in Scheme 1.(19)

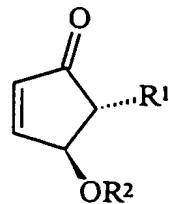
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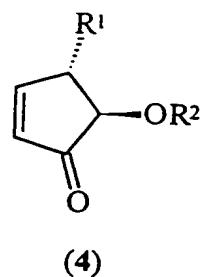
Compounds of type (3) are readily prepared from furfural (Scheme 2). (20)

(3)



Compounds of type (4) are prepared from norbornadiene (Scheme 3). (21)

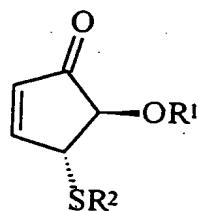
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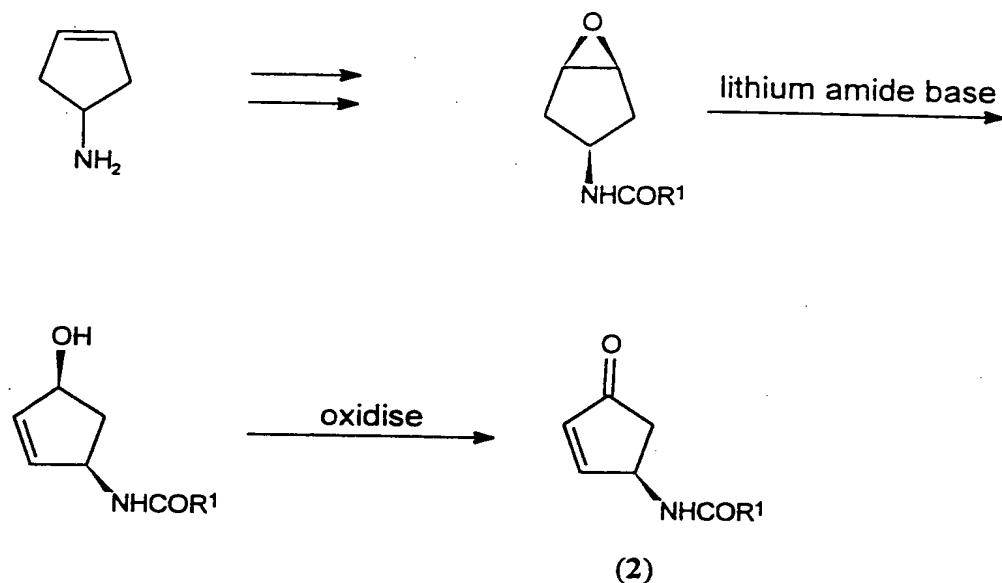
Finally compounds of type (5) are prepared as shown in Scheme 4. (22)

15



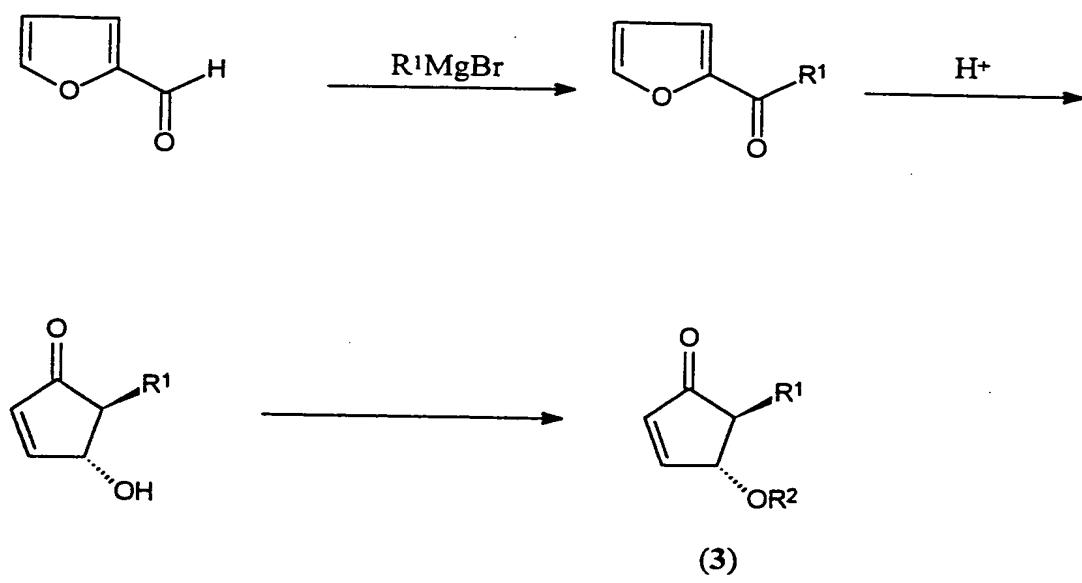
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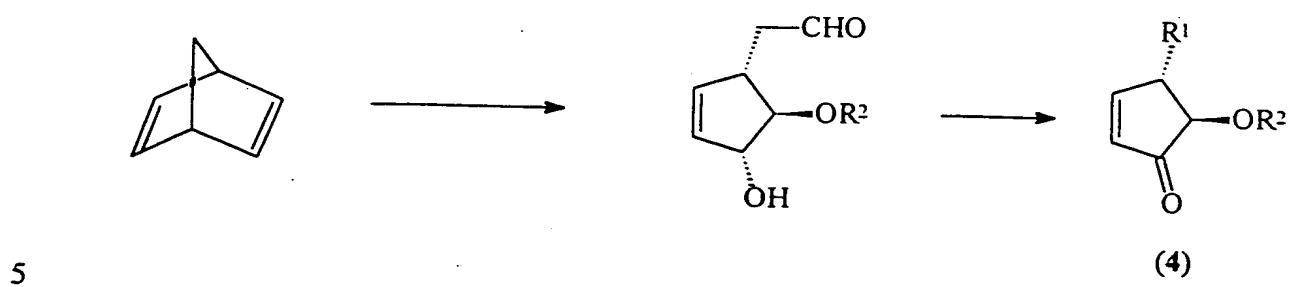
Scheme 1

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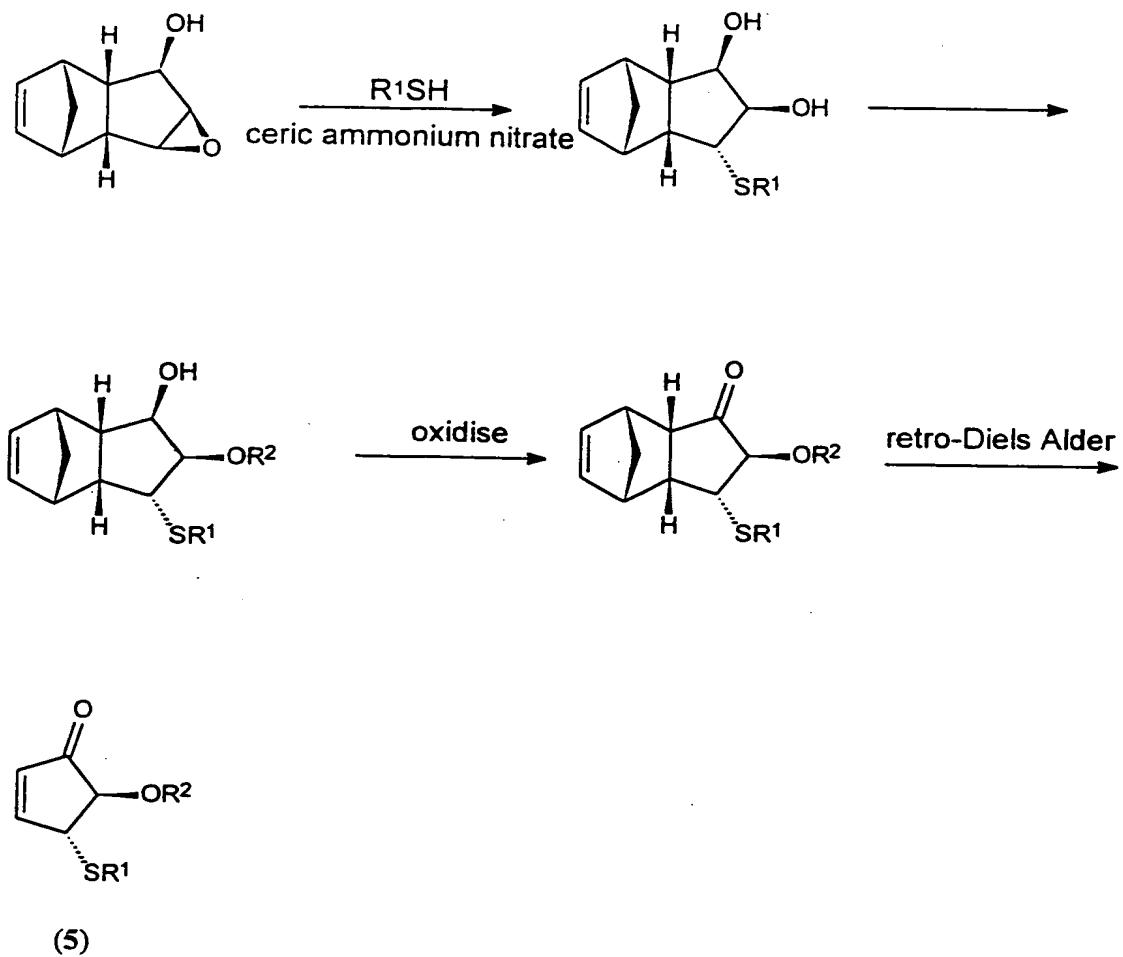


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Scheme 2



Scheme 3



Scheme 4

General Remarks

The foregoing description of the invention is merely illustrative thereof and it should therefore be appreciated that various variations and modifications can be made without departing from the spirit or scope of the invention as set forth in the accompanying claims.

Where preferred or optional features are described in connection with particular aspects of the present invention, they shall be deemed to apply *mutatis mutandis* to other aspects of the invention unless the context indicates otherwise.

All documents cited herein are hereby incorporated by reference, as are any citations referred to in said documents.

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Claims

1. A compound for use in medicine, that has the formula a), b), c) or d), as shown in Figure 1; wherein R₁, R₂, R₃, R₄, R₅ and R₆ are (independently) hydrogen or any other moiety, with the proviso that the compound is not the compound shown in Figure 3b).

5

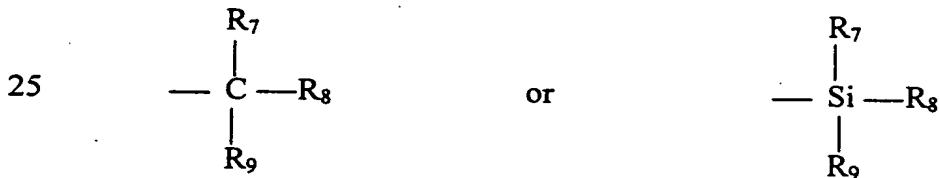
2. A compound for use in medicine according to claim 1, wherein R₁, R₂, R₃ and R₄ are (independently) hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heteroaromatic or 10 heteroalicyclic.

15

3. A compound for use in medicine according to claim 1 or claim 2, wherein X is an Si-containing group.

20

4. A compound for use in medicine according to any preceding claim, wherein X has the formula



30 and wherein R₇, R₈ and R₉ are defined as for R₁, R₂, R₃ and R₄ in claim 1 or claim 2.

5 A compound for use in medicine according to claim 4, wherein R₇, R₈ and R₉ are substituted alkyl, aryl or substituted aryl.

6. A compound for use in medicine according to any preceding claim, wherein X
5 comprises at least 4 carbon atoms.

7. A compound for use in medicine according to any preceding claim, wherein R₅
and R₆ are independently hydrogen or halogen.

10 8. A compound for use in medicine according to any preceding claim, wherein if a
side chain is present at positions R₃ and/or R₄ shown in Figure 1, then it has no more
than 7 carbon atoms.

15 9. A compound for use in medicine according to any of claims 1 to 7, wherein a
hydrocarbyl side chain is not present at positions R₃ and/or R₄ shown in Figure 1.

10 10. A compound for use in medicine according to claim 9, wherein R₃ and/or R₄
shown in Figure 1 are hydrogen.

20 11. A compound for use in medicine according to claim 1 that is a compound as
shown in Fig 2 a) or b)

12. A compound for use in medicine according to any preceding claim that is an S-
enantiomer.

25 13. A compound for use in medicine according to any preceding claim, wherein the
compound has higher activity than cyclopent-2-en-1-one in respect of one or more of
the following:

30 a) activating HSF

- b) inhibiting NF-κB
- c) inhibiting the replication of HSV-1
- d) inhibiting the replication of Sendai virus.

5 14. The use of a compound in the preparation of a medicament for treating a viral-mediated disorder, wherein the compound is as described in any of claims 1 to 13.

10 15. The use of a compound in the preparation of a medicament for treating a bacterial-mediated disorder, wherein the compound is as described in any of claims 1 to 13.

16. The use of a compound in the preparation of a medicament for treating a disorder mediated by radiation, wherein the compound is as described in any of claims 1 to 13.

15 17. The use of a compound in the preparation of a medicament for treating an inflammatory disorder, wherein the compound is as described in any of claims 1 to 13.

18. The use of a compound in the preparation of a medicament for treating a disorder of the immune system, wherein the compound is as described in any of claims 1 to 13.

20

19. The use of a compound in the preparation of a medicament for treating ischemia, wherein the compound is as described in any of claims 1 to 13.

25

20. The use of a compound in the preparation of a medicament for treating arteriosclerosis, wherein the compound is as described in any of claims 1 to 13.

21. The use of a compound in the preparation of a medicament for treating a disorder involving cell proliferation, wherein the compound is as described in any of claims 1 to 13.

22. The use according to claim 21, wherein the disorder is a cancer

23. The use of a compound in the preparation of a medicament for treating a disorder involving damage to cells or killing of cells, wherein the compound is as described in any of claims 1 to 13.

24. The use of a compound in the preparation of a medicament for treating diabetes, wherein the compound is as described in any of claims 1 to 13.

10 25. The use of a compound as a research tool for the analysis of one or more of the following: HSF, NF- κ B, the heat shock response, viral replication, viral-mediated disorders, bacterial-mediated disorders, disorders mediated by radiation (e.g. by UV-radiation), inflammatory disorders, disorders of the immune system, 15 ischemia, arteriosclerosis, disorders involving cell proliferation, disorders involving damage to, or killing of cells, or diabetes; wherein the compound is as described in any of claims 1 to 13.

20 26. A compound that is a compound as described in any preceding claim with the proviso that the compound is not 4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one or 15-deoxy-13,14-dihydroprostaglandin J₂.

25 27. A pharmaceutical composition comprising a compound as described in any preceding claim and optionally including a pharmaceutically acceptable carrier

28. The invention as substantially hereinbefore described

Abstract**Chemical compounds and their uses**

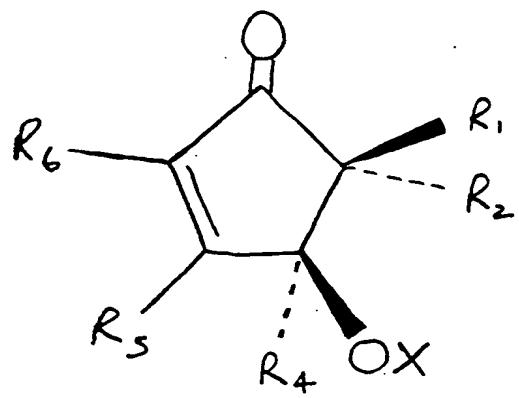
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4- and 5-oxacyclopent-2-en-1-ones have significant activity in activating HSF and in inhibiting NF- κ B. They are believed to be useful in treating a wide range of disorders including viral-mediated disorders, bacterial-mediated disorders, disorders mediated by radiation (e.g. by UV-radiation), inflammatory disorders, disorders of the immune system, ischemia, arteriosclerosis, disorders involving cell proliferation (e.g. cancers), disorders involving damage to, or killing of cells (e.g. oxidative cell damage) and diabetes.

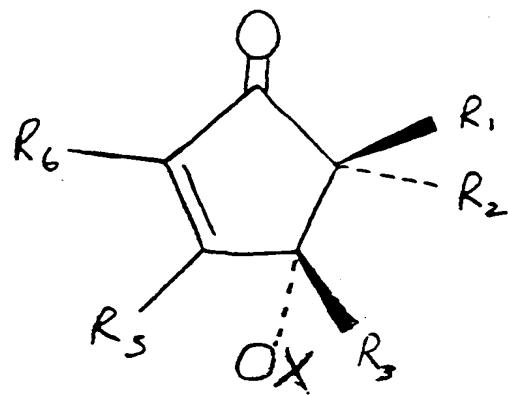
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FIGURE 1

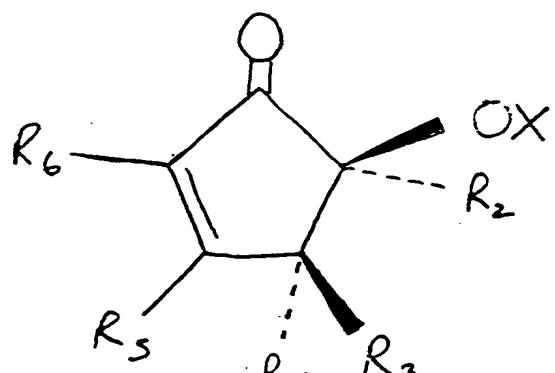
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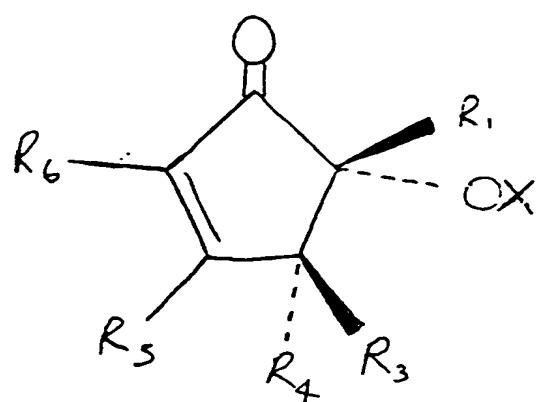
b)



c)



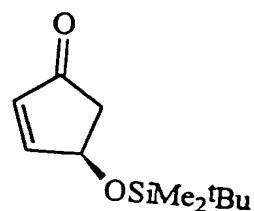
d)



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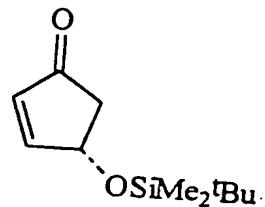
FIGURE 2

a)



R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one

b)

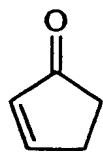


S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one

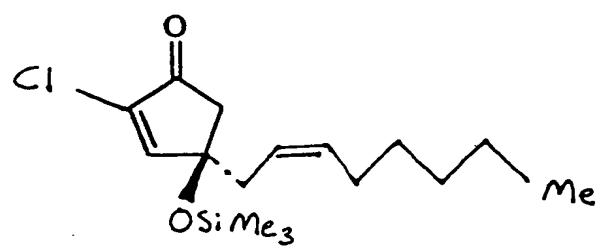
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FIGURE 3

a)

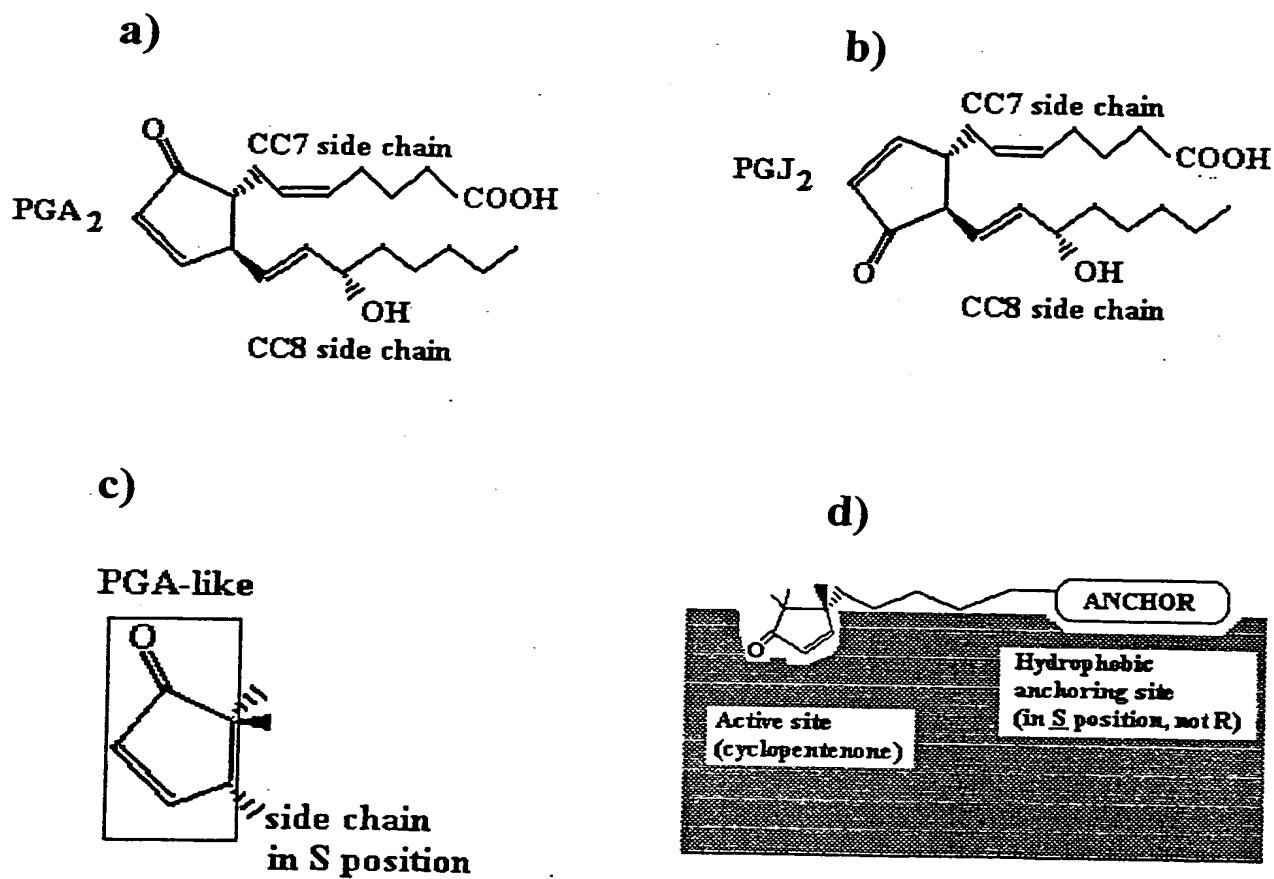


b)



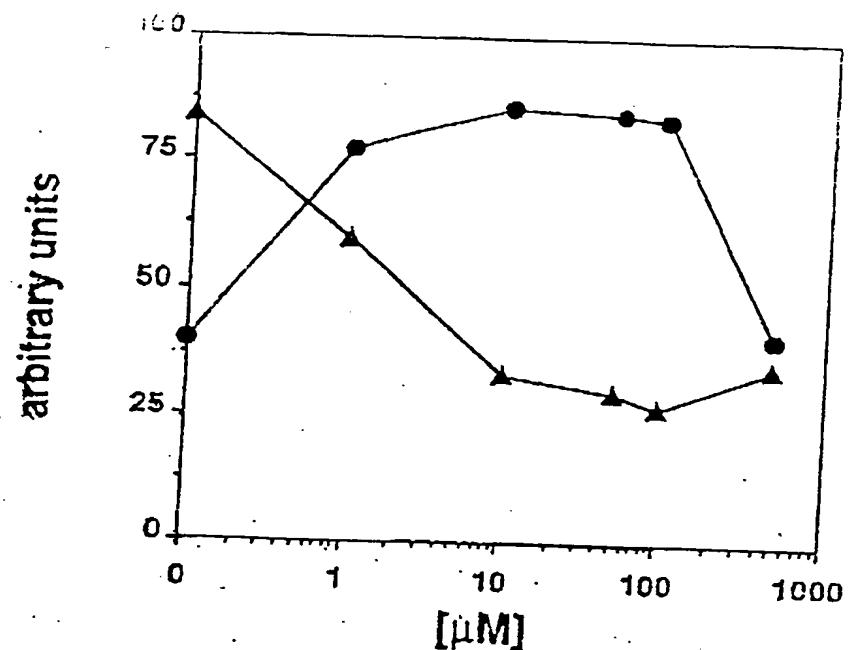
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FIGURE 4

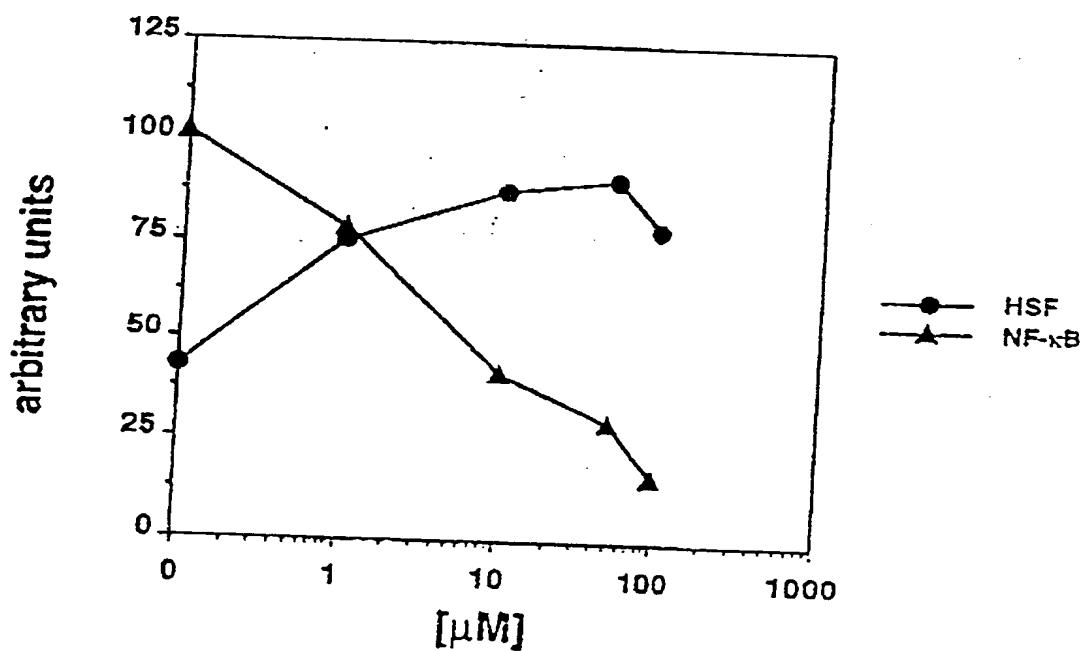


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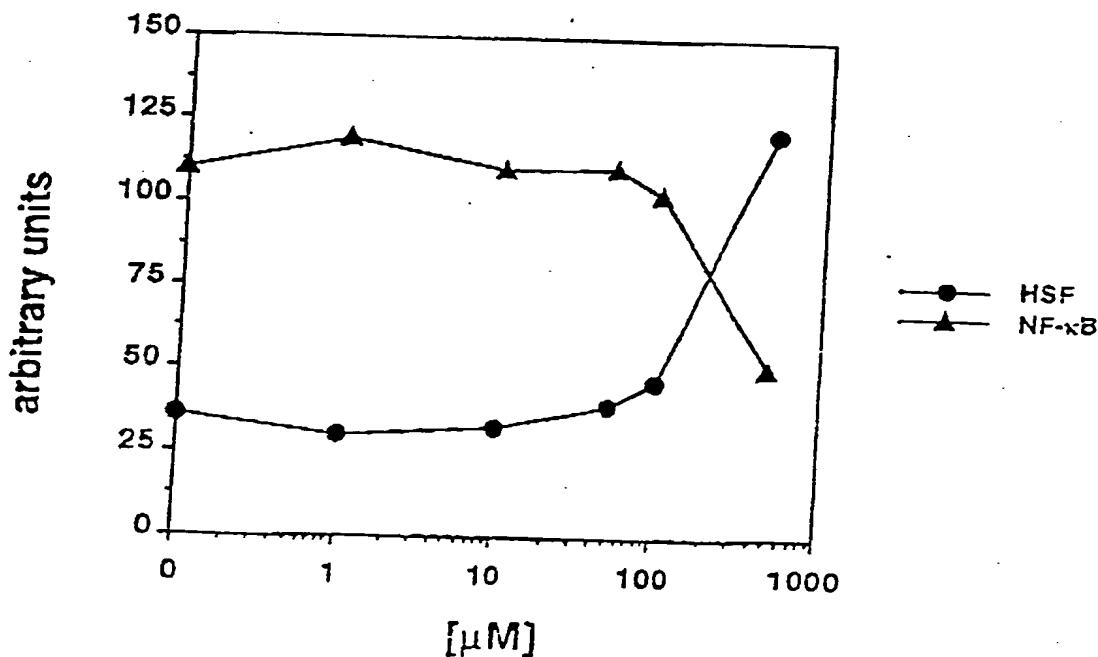
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Sample: CTC 7

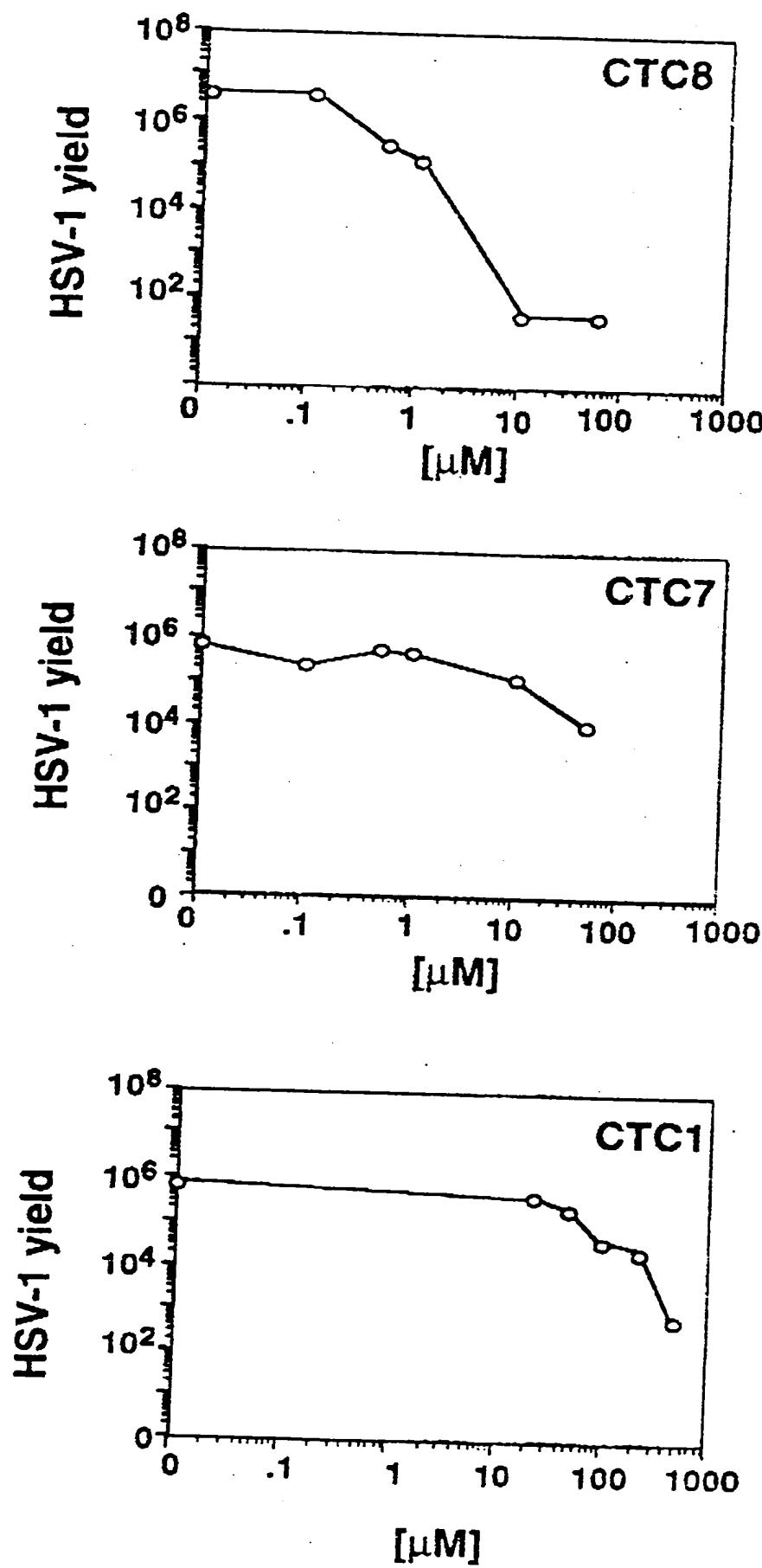


Sample: CTC 1



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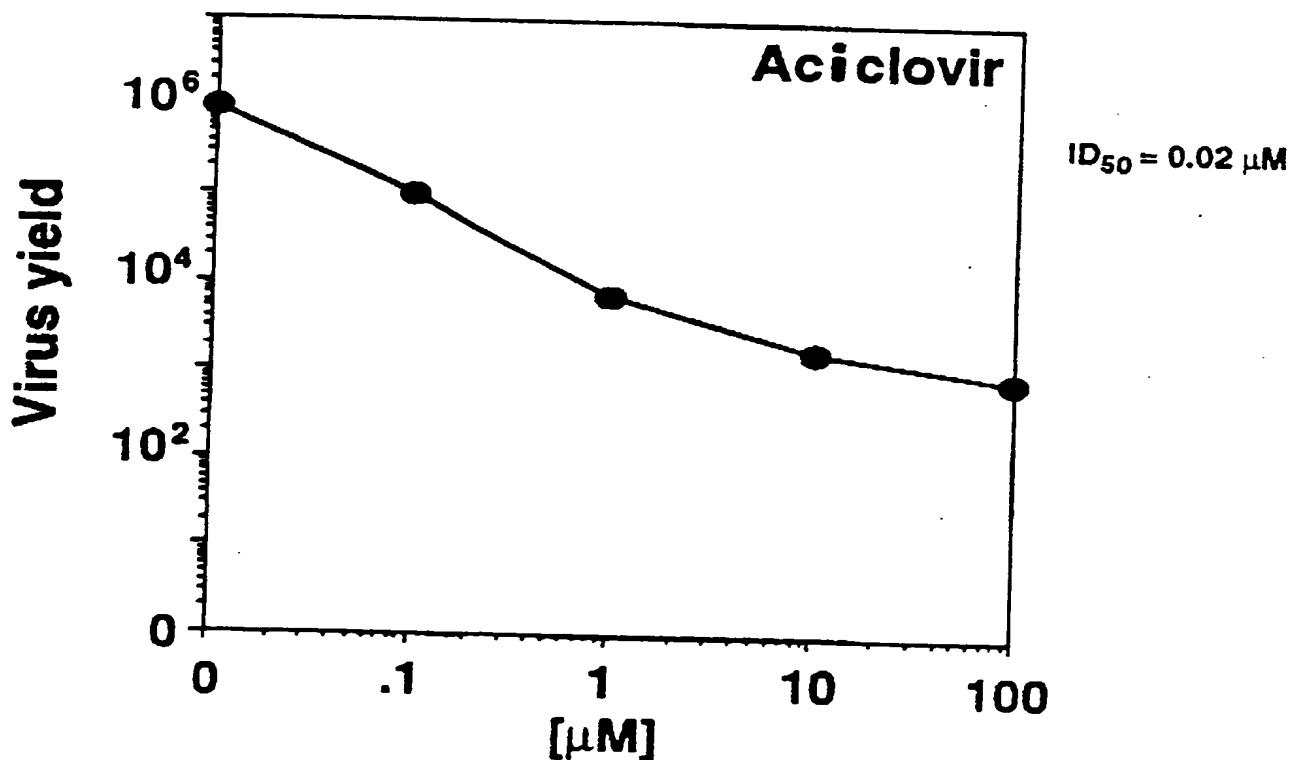
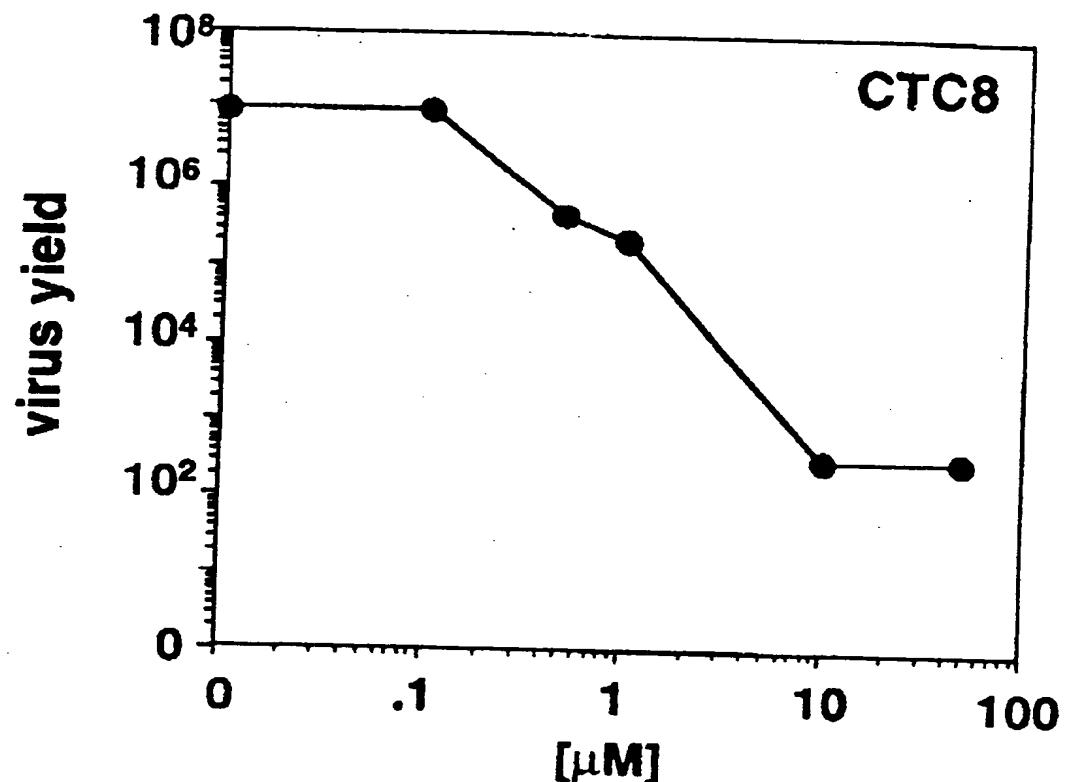
FIGURE 6a)



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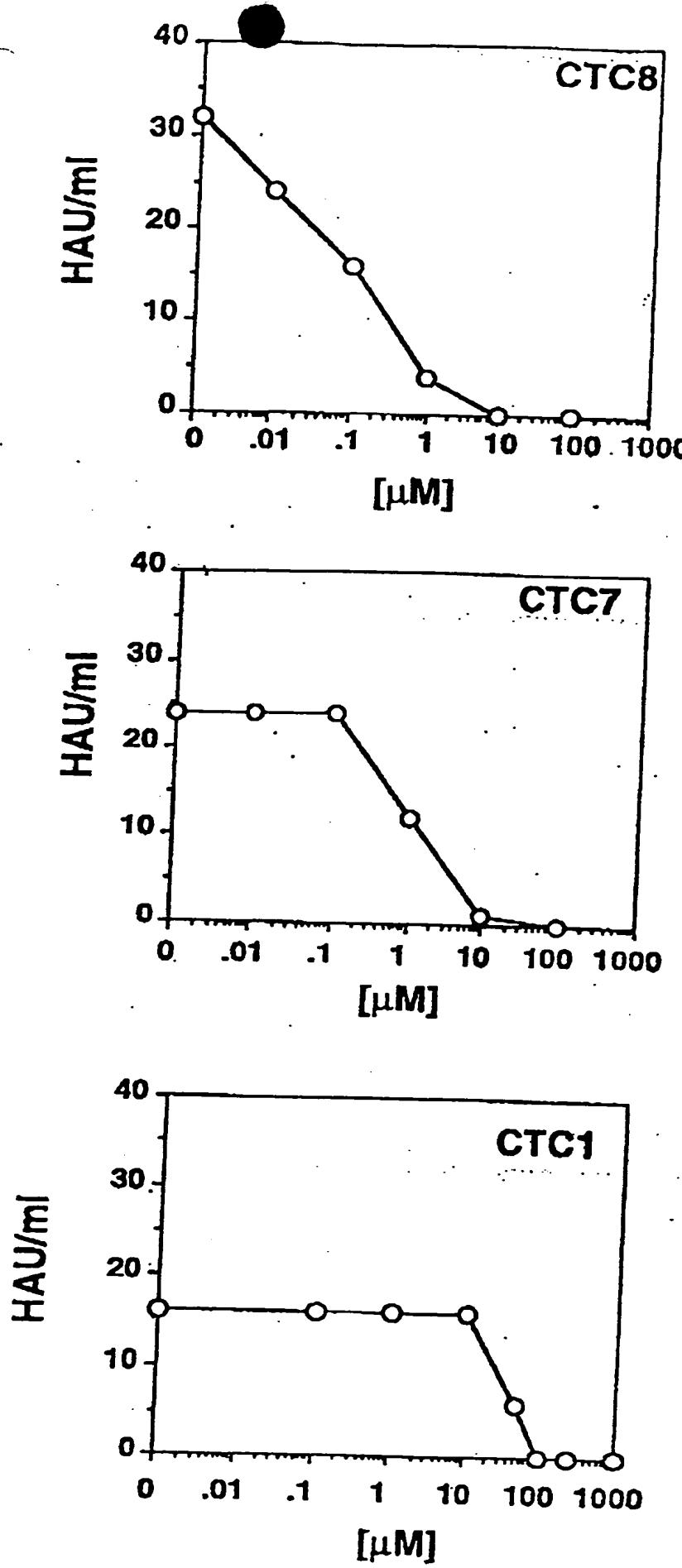
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FIGURE 6b)



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FIGURE 7



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Inhibition of induction of iNOS
by PG-J2 or CTC-8 in mouse macrophages

NO production (% of control)

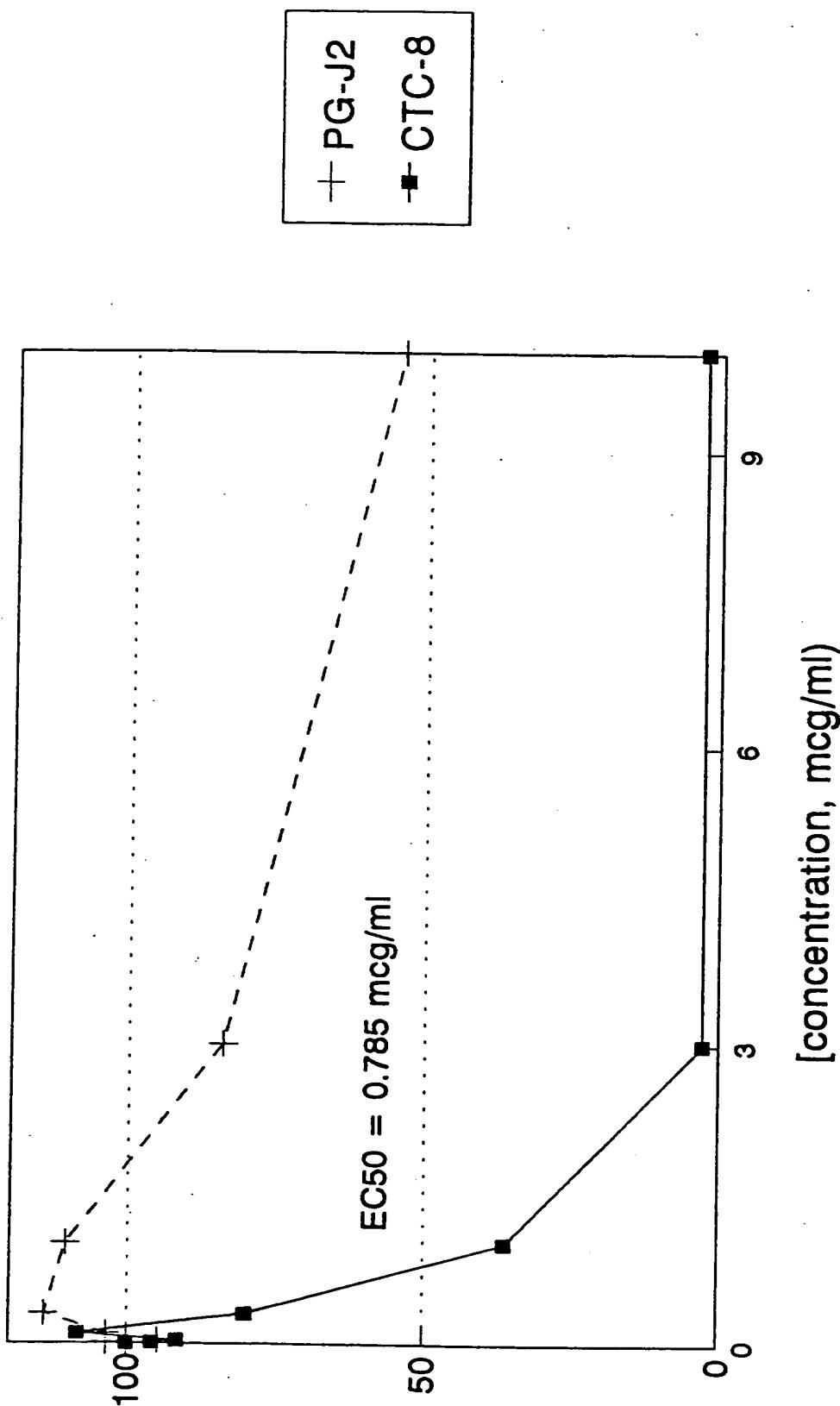
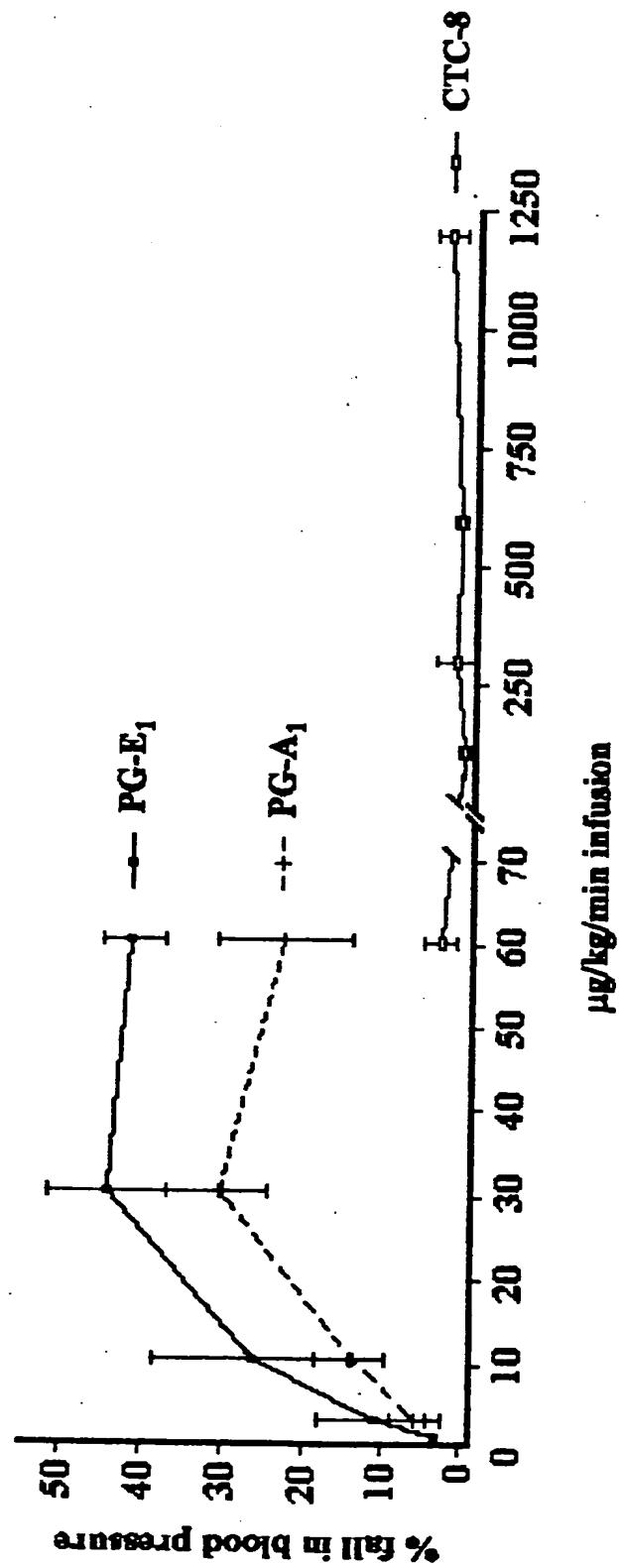


FIGURE 8

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FIGURE 9

Effect of intravenous infusion of CTC-8 on blood pressure of normal Wistar rats



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